

Surgical Treatment of Lung Metastases: Prognostic Factors for Long-Term Survival

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Background and Objectives: Surgical resection of lung metastases is an established therapy for a large number of primary tumors, but there is some controversy about prognostic factors for long-term survival.

Methods: From 1968 to 1996, we performed a retrospective review of a series of 85 patients (100 operations) that have been operated for resection of lung metastases. The Kaplan-Meier method was used to estimate the probabilities of survival, the log-rank test for the univariate analysis of prognostic factors for survival, and the Cox model in the subsequent multivariate analysis.

Results: The operative mortality was 4% and the morbidity 18%. The mean follow-up after lung resection was 22.13 months (1–146). The actuarial 5-year survival rate was 29.2%. By univariate analysis, the following factors were associated with survival after resection: location and histology of the primary tumor, greatest dimension of the largest metastasis, radicality of the resection, involvement of the resection margins, and use of adjuvant therapy ($P < 0.05$). After multivariate analysis, only the dimension of the metastases and involvement of surgical margins have been found to be independently associated with survival.

Conclusions: Surgical excision is a safe and effective therapy for lung metastases from a large number of primary tumors, provided a complete resection is feasible.

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KEY WORDS: surgery; lung metastases; prognostic factors

INTRODUCTION

Either because lung metastases can be a regional disease or because their resection can alter the immunological equilibrium in favor of the host, resection of lung metastases has been actively pursued since the first description of long-term survival after surgical resection of a pulmonary metastasis from a renal cell carcinoma by Barney and Churchill in 1919 [1]. What are the prognostic factors for long-term survival after surgical resection of lung metastases? This is still a controversial issue with different series eliciting different and sometimes contradictory results [2–8]. We retrospectively analyzed our series of lung resections for metastases to try to find the relevant factors in the determination of survival after surgery.

MATERIALS AND METHODS

From January 1968 to December 1996 in our Department of Surgery, 85 adult patients underwent resection of lung metastases from different primary tumors. All patients had been exhaustively evaluated to exclude locally recurrent or extra pulmonary metastatization not amenable to complete resection. All lung disease was assessed as resectable preoperatively by the surgeon and the patients had respiratory function test results compatible with the

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proposed resection. Since 1980, all patients had a preoperative thoracic and, when appropriate, neck, abdominal, and/or pelvic computed tomographic (CT) scans. There were 41 men (48.2%) and 44 women (51.8%), with a mean age of 48.55 years (16–79). They were submitted to 100 thoracotomies (72 patients were operated once, 11 twice, and 2 patients were operated three times). The primary tumors were 18 soft tissue sarcomas, 13 bone sarcomas, 12 squamous cell carcinomas of the head and neck, 10 breast carcinomas, 7 colorectal carcinomas, 5 cervical carcinomas, 4 malignant melanomas, 3 kidney carcinomas, 3 bladder carcinomas, 2 uterine leiomyosarcomas, 2 endometrial carcinomas, and 1 each malignant adamantinoma, adenoid cystic carcinoma of the parotid, maxillary cylindroma, lymphoma, hydatidiform mole, and teratocarcinoma of the testis.

The mean follow-up of the patients after lung resection is 22.13 months (1–146). Only 7 patients (8.2%) were lost to follow-up before death or at the time when the analysis was made.

The Kaplan-Meier product limit method [9] was used to estimate the probability of overall survival after surgery, the log-rank test [10] for the univariate analysis of prognostic factors of survival (PFS), and the Cox proportional-hazards model [11] in the subsequent multivariate analysis. A value of $P < 0.05$ was considered statistically significant.

The evaluated variables were location of the primary tumor, its histology, stage, disease-free interval (DFI), bilaterality of the metastases, number, lung distribution, diameter, type of lung resection, surgical approach, radicality of the resection, surgical margin involvement (based on histologic examination), lymph node involvement, number of thoracotomies, morbidity after lung resection, and use of adjuvant therapies.

The metastases were unilateral in 83 patients (89.2%) and bilateral in 10 (10.8%). They were synchronous (DFI < 12 months) in 21 patients (22.6%) and metachronous in 72 (77.4%). They were single in 63 patients. Twelve patients had 2 metastases, 4 patients 3, 6 patients 4, 1 patient 6, and 3 patients 7 metastases each.

The surgical approach was a posterolateral thoracotomy in 86 patients, 6 staged bilateral thoracotomies, 1 “clamshell” incision, and 1 thoracoscopic resection. There were 81 atypical resections, 3 segmentectomies, 48 lobectomies, 11 bilobectomies, and 3 left pneumonectomies.

Fifty-three patients did not receive any adjuvant therapy, 25 patients had adjuvant chemotherapy, 7 patients adjuvant radiotherapy, 6 patients hormonal therapy, 2 patients hormonal therapy and chemotherapy, and 1 patient hormonal therapy and radiotherapy. The decision about the use of adjuvant therapy was left to the discretion of the attending physicians and was based on the radicality of the resection (radiotherapy) and the chemo-

TABLE I. Major Morbidity after Lung Resection for Metastases

Morbidity	No. of patients ($n = 100$)
Atelectasy	4
Inferior respiratory infections	3
Bronchopleural fistula	2
Hemothorax	2
Pulmonary embolism	2
Respiratory insufficiency	1
Supraventricular tachydysrhythmia	1
Transitory ischemic accident	1
Pleural effusion	1
Deep infection of the operative wound	1
Total	18(18%)

sensitivity of the primary tumor (chemotherapy and hormonal therapy).

RESULTS

Four patients died during their hospital admission (4%). One patient died with a bronchopleural fistula, another from pulmonary embolism, and 2 patients, operated during the early years of our series, died intraoperatively from uncontrolled hemorrhage. Eighteen (18%) patients experienced major morbidity after lung resection for metastases (Table I).

The calculated overall survival rate at 5 years after surgery for lung metastases of the present series is 29.2% (Fig. 1). By univariate analysis, the following factors were associated with prognosis after resection of lung metastases: location of the primary tumor (Table II), histology of the primary tumor, greatest dimension of the largest metastasis ($<Vs> 4$ cm, Fig. 2), radicality of the resection, involvement of resection margins (Fig. 3), and use of adjuvant therapy (Table III). The stage of the primary tumor, synchronous Vs metachronous diagnosis of the metastasis, unilateral Vs bilateral metastases, number of metastases resected ($<Vs> 3$, Fig. 4) and their distribution, surgical approach, type of lung resection, number of thoracotomies, and lymph node metastization in the hilum or mediastinum (Fig. 5) were not found to be significant prognostic factors. After multivariate analysis, only the dimension of the metastases and involvement of surgical margins have been found to be independently associated with survival after lung resection for metastases (Table IV).

DISCUSSION

The accepted criteria for resection of lung metastases have been [5] (1) pulmonary disease completely resectable; (2) absence of nonresectable locally recurrent or metastatic disease in other organs; (3) pulmonary function compatible with the proposed resection; and (4) absence of other more effective therapies available.

Using these criteria, we as many others in the literature obtained a long-term (5 years) survival rate of around

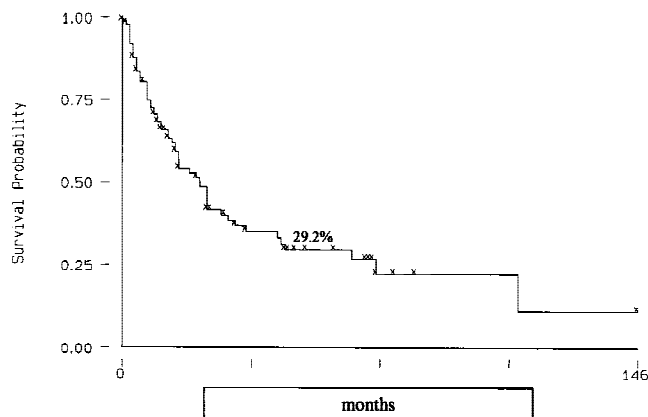


Fig. 1. Kaplan-Meier survival curve: Overall survival in months after lung resection for metastases.

TABLE II. Five-Year Survival in Months after a Lung Resection for Metastases According to Primary Tumor Location (Kaplan-Meier Product Limit Method)

Primary tumor location	No.	5-year survival rate ^{a,b}	Standard error of the mean
Lymphoma	1	100%	0.00
Soft tissue	25	43.67%	12.01
Head and neck	15	30.81%	12.41
Bone	17	27.45%	11.23
Urinary tract	6	16.67%	15.21
Colon and rectum	9	100% (36 months)	0.00
Breast	11	0% (47 months)	0.00
Female genital tract	13	0% (46 months)	0.00
Skin	3	0% (5 months)	0.00

^aLongest survival in parentheses when there were no 5-year survivors.

^bLog-rank: $P = 0.001$.

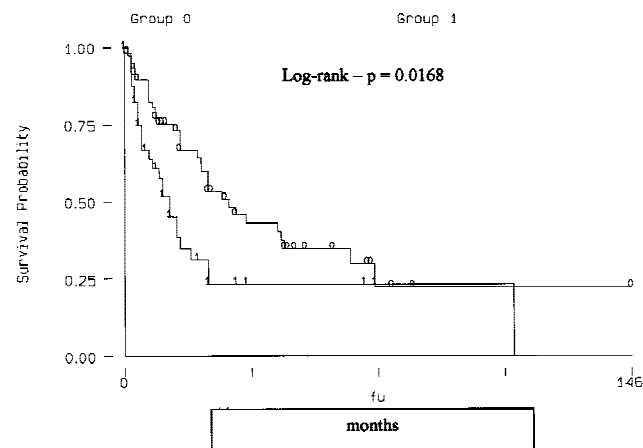


Fig. 2. Kaplan-Meier survival curve: Survival in months after lung resection for metastases according to dimension of the largest metastasis (<4 vs. >4 cm). Line 0 = <4 cm, line 1 = >4 cm.

30% (29.2%) in patients submitted to lung resection for metastases. These are astonishingly good results for a local therapy of a disseminated disease. They compare very favorably with all other therapeutic alternatives,

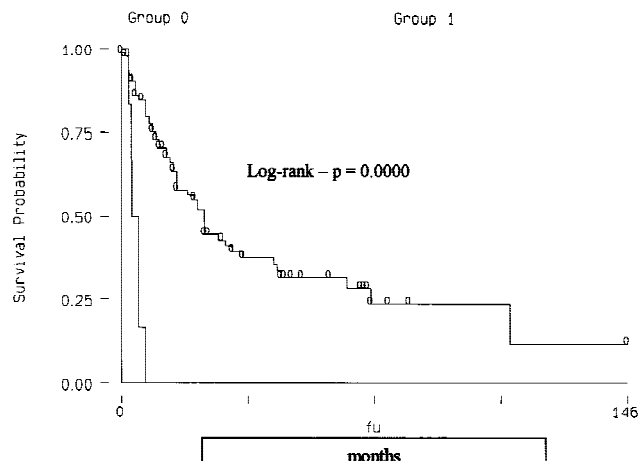


Fig. 3. Kaplan-Meier survival curve: Survival in months after lung resection for metastases according to histologic involvement of resection margins. Line 0 = resection margins not involved, line 1 = resection margins involved.

TABLE III. Five-Year Survival in Months after Lung Resection for Metastases According to Adjuvant Therapy (Kaplan-Meier Product Limit Method)

Adjuvant therapy	No.	5-year survival rate ^{a,b}	Standard error of the mean
None	53	36.78%	0.0776
Chemotherapy	26	38.78%	0.1133
Radiotherapy	9	0% (45 months)	0.1233
Chemo- and radiotherapy	1	0% (4 months)	0.0000
Hormonal therapy	6	0% (12 months)	0.0000
Radiotherapy and hormonal therapy	1	0% (4 months)	0.0000
Chemotherapy and hormonal therapy	2	0% (47 months)	0.0000

^aLongest survival in parentheses when there were no 5 year survivors.

^bLog-rank: $P = 0.0011$.

even considering that this is a very selected group of patients with lung disease that is amenable to complete surgical resection [12–20]. Another remarkable fact is that these results did not deteriorate when the indications for surgical resection were progressively broadened in terms of the number of metastases resected [21,22], the DFI between the treatment of the primary tumor and the diagnosis of lung metastases [7,22–25], bilaterality [7,21,26], type of lung resection [27], and repeated thoracotomies for resection of recurrent pulmonary metastases, as far as complete resection is achievable [15,21,24,26,28,29]. This is true for a very heterogeneous group of tumors, with very different biological characteristics and clinical aggressiveness as can be perceived by review of the published literature, either in a series with metastases of different primary tumors, as the present one [2–5,7,26,30], or in a series of lung resections for metastases of a single type of primary tumor [8,12,14,15,18–20,22–25,31–41]. Having this in mind,

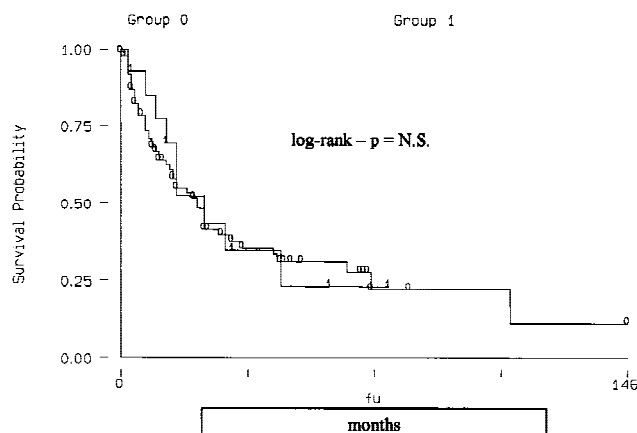


Fig. 4. Kaplan-Meier survival curve: Survival in months after lung resection for metastases according to the number of metastases resected (≤ 3 vs. > 3). Line 0 = ≤ 3 metastases resected, line 1 = > 3 metastases resected. NS = not significant.

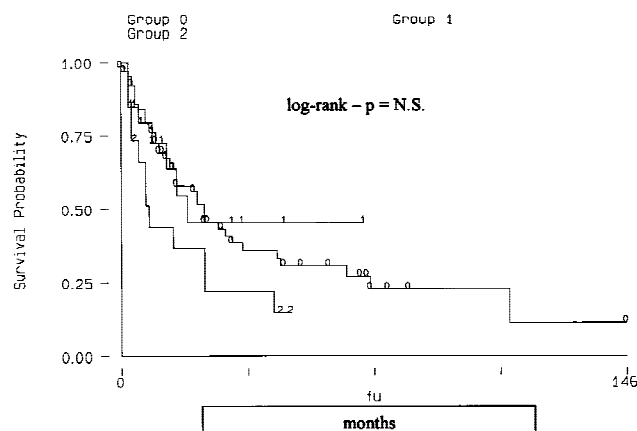


Fig. 5. Kaplan-Meier survival curve: Survival in months after lung resection for metastases according to lymph node metastization. Line 0 = no lymph node resected ($n = 65$), line 1 = lymph nodes resected not involved ($n = 20$), line 2 = lymph nodes resected involved ($n = 15$). NS = not significant.

one cannot help to admit that there is a monotonous behavior of lung metastases from different tumors after complete resection, with a possible exception in our limited experience (but not in other much larger series [42,43]) for malignant melanoma. If this represents that lung metastases can be a regional and not really a systemic disease in a considerable number of patients or that surgical debulking of the tumor can have a beneficial effect in the immunological equilibrium between the tumor and the host is an unresolved debate that can have implications in the future management of this situation [6,20,43,44].

Germ cell tumors (testis, coriocarcinoma) and differentiated thyroid carcinomas are the only groups of primary tumors for which the best treatment for resectable pulmonary metastases is not surgical resection. These lung metastases are so sensitive to the modern protocols

TABLE IV. Significant PFS after Lung Resection for Metastases

	Univariate analysis ^a	Multivariate analysis ^b
Primary tumor location	0.001	NS
Primary tumor histology	0.0078	NS
Diameter of metastases > 4 cm	0.0168	0.05
Radicality of surgery	0.0000	NS
Surgical margin involvement	0.0000	0.002
Adjuvant therapy	0.0011	NS

^aUnivariate analysis was done using the log-rank test.

^bMultivariate analysis was done using the Cox proportional hazards model. NS, not significant.

of chemotherapy and radioactive iodine, respectively, that these are the first choice of treatment and frequently all that is necessary to cure the disease [45–47]. Surgical resection is justified only for residual lung masses after chemotherapy in germ cell tumors that have an equal probability of being metastatic, fibrotic, or a benign teratoma [35,36,45,46,48]. All other resectable pulmonary metastases are best treated by surgery.

The advantage of adjuvant therapies after complete resection of lung metastases is generally not established [7,13,19,33,38,49]. In our experience, we could not find any benefit of postoperative chemotherapy after lung resections for pulmonary metastases (Table III). These results should be interpreted cautiously because this is a retrospective review of patients treated for a variety of primary tumors and without strict criteria for the use of adjuvant therapies. The apparent deleterious effect of postoperative radiotherapy should be attributed to a bias of selection, once the patients who received radiotherapy were those with bulky metastases or involvement of surgical margins.

The prognostic implication of the presence of lymph node metastases in the mediastinum is a very controversial issue [24–26,34] and one that is not easy to solve. To our knowledge there are no published series of lung resections for metastases with systematic mediastinal lymphadenectomy. In our series, as in others [24,25], mediastinal lymph nodes were resected when they were suspected of metastization. We have data about the presence of lymph node metastases in a minority of our patients (35%). Despite the fact that there is a trend for a worse survival in patients with mediastinal involvement (Fig. 5), this difference did not reach statistical significance, possibly due to the small number of patients studied.

As far as the type of resection is concerned, the least resection that achieves complete removal of lung metastases is enough. In our series, there was an evolution from an exclusive use of anatomical resections (mostly lobectomies) to a preference for atypical resections in the last 15 years [2]. In any case, centrally located tumors

still need larger, anatomical resections (lobectomy or pneumonectomy) in order to remove all disease [27].

The surgical approach is another controversial issue, with some authors recommending a bilateral approach through a median sternotomy [49,50]. This is because of the significant contralateral metastization that is not evident in the preoperative staging of the patients but that is detected intraoperatively (45%) [50]. We used mainly a posterolateral thoracotomy for patients with preoperative evidence of unilateral disease [4]. For patients with bilateral disease, we now prefer to use a bilateral antero-lateral thoracotomy with transverse sternotomy (clam-shell incision) [51]. This allows better exposure of both pleural cavities with easy access to every lung segment, including the left lower lobe that is difficult to access through a median sternotomy [21]. The surgical approach has no impact on the survival rate after lung resection for metastases in our series and others [50]. Huth et al. [52] showed that after unilateral resection of lung metastases, there were no more contralateral than ipsilateral recurrences.

Thoracoscopy has also been condemned in the management of patients with lung metastases. It does not allow the manual palpation of all lung parenchyma that frequently reveals the existence of further metastases beyond those that are detected by the preoperative CT scan [30,49]. Despite the fact that we do not use thoracoscopy as an elective approach in patients with lung metastases, it is inevitable that some of the peripheral lung nodules that are currently resected through video-assisted thoracoscopies (VATS) are found to be metastases after histological examination [53,54]. We do not reoperate these patients without evidence of recurrent disease and keep them in the same follow-up program as the other patients operated through a conventional thoracotomy. This follow-up is justified because the detection of recurrent lung metastases is amenable to further surgical resection if the disease can be removed without deterioration of long-term survival of these patients, no matter how many thoracotomies are performed [28,29,55].

CONCLUSIONS

In our experience, the only factors that influence the survival of patients after lung resection for lung metastases are the involvement of surgical margins by the tumor and the greatest dimension of the greatest metastasis ($<V_s > 4$ cm). We believe that surgery is almost always the best treatment for patients with resectable lung metastases. Improvement over the present results will depend on the appearance of novel systemic therapies that will replace surgery as the first approach to these patients (as is already the case with germ cell tumors) or that will prove to be effective as adjuvant therapy after lung resection (what has not yet been established with the current modalities of treatment).

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